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SPECIAL EDITION

REPORT ON RECENT ETS AND IAQ DEVELOPMENTS

EPA DRAFT RISK ASSESSMENT

June 18, 1992

SHB

EPA RELEASES REVISED DRAFT RISK ASSESSMENT ON ETS; SAB SCHEDULES REVIEW FOR JULY 21-22, 1992

DOCUMENT ALLEGES CAUSAL ASSOCIATION BETWEEN ETS AND LUNG CANCER AS WELL AS RESPIRATORY DISEASES IN CHILDREN AND ADULTS

EPA released a revised draft ETS Risk Assessment on Thursday, and the agency's Science Advisory Board has scheduled an open meeting to review the document for July 21-22, 1992, in Arlington, Virginia.

The following appendices are attached:

Appendix A -- The table of contents and opening sections of the revised draft risk assessment, including the "Summary and Conclusions" section.

Appendix B -- The SAB meeting notice, which has been signed and is expected to be published in the Federal Register between June 18 and June 22.

Appendix C -- Background material compiled by Shook, Hardy & Bacon on scientific and technical issues related to the risk assessment.

It is anticipated that the risk assessment could go to the SAB Executive Committee in October and be signed by EPA Administrator William Reilly before the end of 1992. EPA has renamed the document Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. The title of the original draft, issued in 1990, was Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children.

EPA has not released or provided a timetable for release of a revised draft of the Workplace Smoking Policy Guide, which was issued as a companion to the original draft risk assessment.

Revised Draft Risk Assessment -- Findings

The "Summary and Conclusions" section of the revised draft risk assessment includes the following conclusions on the subject of lung cancer in adults:

- "Passive smoking is causally associated with lung cancer in adults, and ETS, by the total weight-of-evidence, belongs in the category of compounds

classified by EPA as Group A (known human) carcinogens."

- "The conclusive evidence of the dose-related lung carcinogenicity of MS [mainstream smoke] in active smokers, coupled with information on the chemical similarities of MS and ETS and evidence of ETS uptake in nonsmokers, is sufficient by itself to establish ETS as a known human lung carcinogen, or 'Group A' carcinogen under U.S. EPA's carcinogen classification system."

- "[T]he overall results of 30 epidemiologic studies on lung cancer and passive smoking, using spousal smoking as a surrogate of ETS exposure for female never-smokers, similarly justify a Group A classification."

- "An estimated range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. The confidence in this range is medium to high with approximately 3,000 annual lung cancer deaths representing the best estimate."

Regarding non-cancer respiratory diseases and disorders in children, the draft concludes as follows:

- "Exposure of children to ETS from parental smoking is causally associated with: increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze); increased prevalence of middle ear effusion (a sign of middle ear disease), and a small but statistically significant reduction in lung function as tested by objective measures of lung capacity."

- Parental smoking is "causally associated with an increased risk of lower respiratory tract infections," including pneumonia, bronchitis and bronchiolitis.

- Parental smoking is estimated to contribute between 150,000 to 300,000 lower respiratory tract infections annually among infants and children, resulting in 7,500 to 15,000 hospitalizations. The estimates are restricted to children under 18 months of age.

- Exposure to ETS is "causally associated with additional episodes and increased severity of asthma in children who already have the disease."

- "ETS exposure exacerbates symptoms in approximately 20 percent of this country's two million to five million asthmatic children and is a major aggravating factor in approximately 10 percent."

- "[T]he epidemiologic evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms."

- "[P]reviously asymptomatic children exposed to ETS from mothers who smoke at least ten cigarettes a day will exhibit a probable range of 8,000 to 26,000 new cases of asthma annually."

Regarding non-cancer respiratory diseases and disorders in adults, the draft contends that "passive smoking has subtle but significant effects on the respiratory health of nonsmoking adults, including coughing, phlegm, chest discomfort, and reduced lung function."

The report also concludes that "while there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS (sudden infant death syndrome), available studies do not allow us to differentiate whether and to what extent this increase is related to in utero versus postnatal exposure to tobacco smoke products."

Finally, the draft finds the evidence "inconclusive" regarding an association of parental smoking with either upper respiratory tract infections (colds and sore throats) or acute middle ear infections in children.

According to the draft's Preface, a comprehensive search of the scientific literature for the revision is complete through September 1991. A few studies published since then were included based on reviewers' recommendations, the Preface stated.

SAB Meeting

The SAB panel which will review the revised draft risk assessment on July 21-22 is the Indoor Air Quality and Total Human Exposure Committee (IAQTHEC), the same committee which held a public hearing on the original draft risk assessment in December 1990. The IAQTHEC's report, issued in April 1991, triggered the revision

process which culminated in Thursday's release of the revised draft risk assessment.

The notice for the upcoming IAQTHEC meeting contains a "Charge to the Committee" -- a list of 15 questions that EPA has asked the committee to answer. "This Charge is subject to change and the Committee may elect to investigate other areas as well," according to the notice.

The notice also outlines procedures for providing comments to the IAQTHEC, although the SAB states that EPA "is not soliciting public comment." Members of the public who wish to make an oral presentation at the meeting on July 21-22 must provide written notification on or before 4 p.m. July 14. Written statements may be submitted at any time up until the meeting; statements received by the SAB by noon on July 6 will be mailed to the IAQTHEC before the meeting.

History of EPA Risk Assessment on ETS

On June 25, 1990, EPA formally released the draft document Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children ("original draft risk assessment"). This document suggested that ETS should be classified as a Group A ("known human") carcinogen, purportedly in accordance with EPA's Guidelines for Carcinogen Risk Assessment. The original draft risk assessment's conclusion was based on 23 epidemiologic studies of nonsmoking women married to smokers (spousal smoking studies). Using the statistical technique of meta-analysis, the original draft risk assessment calculated a statistically significant summary relative risk of 1.41 (95% CI 1.26-1.57).

Moreover, using the data from nonsmoking women, the document calculated that 3,800 lung cancer deaths could be attributed to ETS in the United States each year. With regard to children, the EPA did not conduct a risk assessment, but rather reviewed some of the literature in this area and concluded that ETS exposure was related to certain childhood respiratory ailments.

When the original draft risk assessment was released, EPA announced a public comment period which closed on October 1, 1990. More than 100 comments were submitted on the original draft risk assessment. (An additional 100 comments were submitted on its companion publication, the draft Workplace Smoking Policy Guide.) The public comments were reviewed and summarized by the EPA consultant responsible for the original draft risk assessment. In a document distributed in December 1990, he characterized the majority of the public comments as "quite lengthy, detailed, and highly critical."

In the fall of 1990, the original draft risk assessment was submitted for review to the IAQTHEC, chaired by Dr. Morton Lippmann. Substantial press coverage was devoted to the inclusion of Dr. David Burns, an anti-smoking activist, on the reviewing committee. EPA issued its "charge" to the committee on November 1, 1990. The IAQTHEC met on December 4-5, 1990, in Arlington, Virginia, for a public hearing to receive public comments and to discuss its recommendations concerning the original draft risk assessment.

A number of substantial criticisms and suggestions for revisions to the document were made at that meeting. Nevertheless, at the end of the meeting, Chairman Lippmann announced at a press conference that the IAQTHEC had reached a "consensus" that ETS should be classified as a Group A carcinogen. He added, however, that he felt the alleged cancer risk posed by ETS was less than the risk posed by rush hour traffic in Washington, D.C. As the press conference began, an EPA press liaison stated that Dr. Lippmann was speaking for himself, not the EPA, the SAB, or other SAB members.

During late 1990 and early 1991, the IAQTHEC apparently drafted a written report concerning its review of the original draft risk assessment. The report supported the "Group A" designation, but recommended that EPA revise the original draft risk assessment. IAQTHEC submitted its report to the SAB Executive Committee at a meeting held on April 18-19, 1991. The Executive Committee approved the IAQTHEC report, and it was delivered to EPA Administrator William Reilly on April 23, 1991. Since that time, EPA staff apparently have been revising the document.

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SAB Review Draft

EPA

Respiratory Health Effects of Passive Smoking:

Review Draft

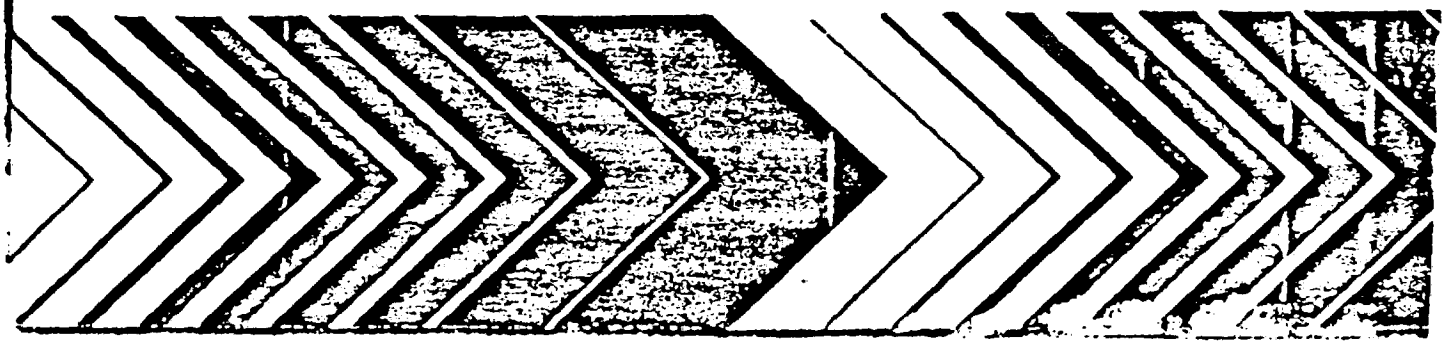
(Do Not Cite or Quote)

Lung Cancer and Other Disorders

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

APPENDIX A



EPA/600/6-90/006B
May 1992
SAB Review Draft

RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS

NOTICE

THIS DOCUMENT IS A PRELIMINARY DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

This report has been supported by the Office of Health and Environmental Assessment, Office of Research and Development, and the Indoor Air Division, Office of Atmospheric and Indoor Air Programs.

Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C.

DISCLAIMER

This document is a draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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PREFACE

This assessment of the respiratory health effects associated with passive smoking has been prepared by the Human Health Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, which is responsible for its scientific accuracy and conclusions. The assessment was prepared at the request of the Indoor Air Division, Office of Atmospheric and Indoor Air Programs, Office of Air and Radiation, which defined its scope and provided funding.

The document has been developed under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

An earlier draft of this document was made available for public review and comments in June 1990, and was reviewed by the Agency's Science Advisory Board in December 1990. This revision reflects the comments received from those reviews, plus additional comments from an internal review conducted in February and March 1992.

A comprehensive search of the scientific literature for this revision is complete through September 1991. In addition, a few studies published since then have been included in response to recommendations made by reviewers.

Due to both resource and time constraints, the scope of this report has been limited to an analysis of respiratory effects, primarily lung cancer in nonsmoking adults and noncancer respiratory illnesses in children, with emphasis on the epidemiologic data. Further, because two thorough reviews on passive smoking were completed in 1986 (by the U.S. Surgeon General and the National Research Council), this document provides a summary of those reports with a more comprehensive analysis of the literature appearing subsequent to those reports and an integration of the results.

It is the Agency's intention with the release of this draft to seek additional advice from its Science Advisory Board in preparation for release of a final report later this year.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

This document was prepared by the Office of Health and Environmental Assessment (OHEA) within the Office of Research and Development, with major contract funding provided by the Indoor Air Division within the Office of Air and Radiation's Office of Atmospheric and Indoor Air Programs. Steven P. Bayard served as OHEA project manager with overall responsibility for contents of this report and its conclusions.

Other OHEA staff responsible for the scientific content of sections of this document are Aparna M. Koppikar[1] and Jennifer Jinot[1]. Jennifer Jinot also served as a contributor and technical editor for a major portion of this report.

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REVIEWERS

This document is a revision of an earlier External Review Draft (EPA/600/6-90/006A) that was released for public review and comment on June 25, 1990. The draft document subsequently was reviewed by the EPA Science Advisory Board (SAB) on December 4 and 5, 1990. Many of the revisions follow closely the valuable advice presented in the SAB's April 19, 1991, report to the Agency. Other revisions are based on comments received from peer reviewers and the public. In addition, many reviewers both within and outside the Agency provided assistance at various internal review stages.

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1. SUMMARY AND CONCLUSIONS

1.1. BACKGROUND

Tobacco smoking has long been recognized (e.g., U.S. DHEW, 1964) as a major cause of mortality and morbidity, responsible for an estimated 434,000 deaths per year in the United States (CDC, 1991a). Tobacco use is known to cause cancer at various sites, in particular the lung (U.S. DHHS, 1982; IARC, 1986). Smoking can also cause respiratory diseases (U.S. DHHS, 1984, 1989) and is a major risk factor for heart disease (U.S. DHHS, 1983). In recent years there has been concern that nonsmokers may also be at risk for some of these health effects as a result of their exposure ("passive smoking") to the tobacco smoke that occurs in various environments occupied by smokers. Although this environmental tobacco smoke (ETS) is dilute compared to the mainstream smoke (MS) inhaled by active smokers, it is chemically similar, containing many of the same carcinogenic and toxic agents.

In 1986, the National Research Council (NRC) and the Surgeon General of the U.S. Public Health Service independently assessed the health effects of exposure to ETS (NRC, 1986; U.S. DHHS, 1986). Both of the 1986 reports conclude that ETS can cause lung cancer in adult nonsmokers and that children of parents who smoke have increased frequency of respiratory symptoms and acute lower respiratory tract infections, as well as evidence of reduced lung function.

More recent epidemiologic studies of the potential associations between ETS and lung cancer in nonsmoking adults and between ETS and noncancer respiratory effects more than double the size of the database available for analysis from that of the 1986 reports. This U.S. EPA document critically reviews the current database on the respiratory health effects of passive smoking, and these data are utilized to develop a hazard identification for ETS and to make quantitative estimates of the public health impacts of ETS for lung cancer and various other respiratory diseases.

The weight-of-evidence analysis for the lung cancer hazard identification is developed in accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a) and established principles for evaluating epidemiologic studies. The analysis considers animal bioassays and genotoxicity studies, as well as biological measurements of human uptake of tobacco smoke components and epidemiologic data on active and passive smoking. The availability of abundant and consistent human data, and especially human data at actual environmental levels of exposure to the specific agent (mixture) of concern, allow a hazard identification to be made with

a high degree of certainty. The conclusive evidence of the dose-related lung carcinogenicity of MS in active smokers (Chapter 4), coupled with information on the chemical similarities of MS and ETS and evidence of ETS uptake in nonsmokers (Chapter 3), is sufficient by itself to establish ETS as a known human lung carcinogen, or "Group A" carcinogen under U.S. EPA's carcinogen classification system. In addition, this document concludes that the overall results of 30 epidemiologic studies on lung cancer and passive smoking (Chapter 3), using spousal smoking as a surrogate of ETS exposure for female never-smokers, similarly justify a Group A classification.

The weight-of-evidence analyses for the noncancer respiratory effects are based primarily on a review of epidemiologic studies (Chapter 7). Most of the endpoints examined are respiratory disorders in children, where parental smoking is used as a surrogate of ETS exposure. For the noncancer respiratory effects in nonsmoking adults, most studies used spousal smoking as an exposure surrogate. A causal association was concluded to exist for a number of respiratory disorders where there was sufficient consistent evidence for a biologically-plausible association with ETS that could not be explained by bias, confounding, or chance. The fact that the database consists of human evidence from actual environmental exposure levels gives a high degree of confidence in this conclusion. Where there was suggestive but inconclusive evidence of causality, as was the case for asthma induction in children, ETS was concluded to be a risk factor for that endpoint. Where data were inconsistent or inadequate for evaluation of an association, as for acute upper respiratory tract infections and acute middle ear infections in children, no conclusions were drawn.

This report has also attempted to provide estimates of the extent of the public health impact, where appropriate, in terms of numbers of ETS-attributable cases in nonsmoking subpopulations. Unlike for qualitative hazard identification assessments where information from many sources adds to the confidence in a weight-of-evidence conclusion, for quantitative risk assessments the usefulness of studies usually depends on how closely the study population resembles nonsmoking segments of the general population. For lung cancer estimates among U.S. nonsmokers, the substantial epidemiology database of ETS and lung cancer among U.S. female never-smokers was considered to provide the most appropriate information. From the large number of similarly designed studies, pooled relative risk estimates were calculated and used in the derivation of the population risk estimates. The large number of studies available, the generally consistent results, and the condition of actual environmental levels of exposure increase the confidence in these estimates. Even with these conditions, however, uncertainties remain, such as in the use of questionnaires and current biomarker measurements to estimate past

exposure, assumptions of exposure-response linearity, and extrapolation to male never-smokers and to exsmokers. Still, given the strength of the evidence for the lung carcinogenicity of tobacco smoke and the extensive human database from actual environmental exposure levels, fewer assumptions are necessary than is usual in U.S. EPA quantitative risk assessments and confidence in these estimates is rated medium to high.

Population estimates of ETS health impacts are also made for certain noncancer respiratory endpoints in children, specifically lower respiratory tract infections (LRIs, i.e. pneumonia, bronchitis, and bronchiolitis) and episodes and severity of attacks of asthma. Estimates of ETS-attributable cases of LRI in infants and young children are thought to have a high degree of confidence because of the consistent study findings and the appropriateness of parental smoking as a surrogate measure of exposure in very young children. Estimates of the number of asthmatic children whose condition is aggravated by exposure to ETS are less certain than those for LRIs because of different measures of outcome in various studies and because of increased extraparental exposure to ETS in older children. Estimates of the number of new cases of asthma in previously asymptomatic children also have less confidence because at this time the weight-of-evidence for asthma induction, while suggestive of a causal association, is not conclusive.

Most of the ETS population impact estimates are presented in terms of ranges, which are thought to reflect reasonable assumptions about the estimates of parameters and variables required for the extrapolation models. The validity of the ranges is also dependent on the appropriateness of the extrapolation models themselves.

While this report focuses only on the respiratory health effects of passive smoking, there may also be other health effects of concern. Recent analyses of more than a dozen epidemiology and toxicology studies (Steenland, 1992; NIOSH, 1991) suggest that ETS exposure may be a risk factor for cardiovascular disease. In addition, there were a few studies in the literature linking ETS exposure to cancers of others sites; at this time, that database appears inadequate for any conclusion. This report does not develop an analysis of either the nonrespiratory cancer or the heart disease data and takes no position on whether ETS is a risk factor for these diseases. If it is, the total public health impact from ETS will be greater than that discussed here.

1.2. PRIMARY FINDINGS

A. Lung Cancer in Nonsmoking Adults

1. Passive smoking is causally associated with lung cancer in adults, and ETS, by the total weight-of-evidence, belongs in the category of compounds classified by EPA as Group A (known human) carcinogens.
2. An estimated range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. The confidence in this range is medium to high with approximately 3,000 annual lung cancer deaths representing the best estimate.

B. Noncancer Respiratory Diseases and Disorders

1. Exposure of children to ETS from parental smoking is causally associated with:
   a. increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze),
   b. increased prevalence of middle ear effusion (a sign of middle ear disease), and
   c. a small but statistically significant reduction in lung function as tested by objective measures of lung capacity.
2. ETS exposure of young children and particularly infants from parental (and especially mother's) smoking is causally associated with an increased risk of lower respiratory tract infections (pneumonia, bronchitis, and bronchiolitis). This report estimates that exposure to ETS contributes 150,000 to 300,000 lower respiratory tract infections annually in infants and children less than 18 months of age, resulting in 7,500 to 15,000 hospitalizations. These higher risks continue at a decreasing rate for children until about age 3, but no estimates are derived for children over 18 months.
3. a. Exposure to ETS is causally associated with additional episodes and increased severity of asthma in children who already have the disease. This report estimates that ETS exposure exacerbates symptoms in approximately 20% of this country's 2 million to 5 million asthmatic children and is a major aggravating factor in approximately 10%.

b. In addition, the epidemiologic evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms. Based on this evidence and the known ETS effects on both the immune system and lungs (e.g. atopy and airway hyperresponsiveness), this report concludes that ETS is a risk factor for the induction of asthma in previously asymptomatic children. Data suggest that relatively high levels of exposure are required to induce new cases of asthma in children. This report estimates that previously asymptomatic children exposed to ETS from mothers who smoke at least 10 cigarettes per day will exhibit a probable range of 8,000 to 26,000 new cases of asthma annually. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

4. Passive smoking has subtle but significant effects on the respiratory health of nonsmoking adults, including coughing, phlegm, chest discomfort, and reduced lung function.

This report also has reviewed data on the relationship of maternal smoking and sudden infant death syndrome (SIDS), which is thought to involve some unknown respiratory pathogenesis. The report concludes that while there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS, available studies do not allow us to differentiate whether and to what extent this increase is related to in utero versus postnatal exposure to tobacco smoke products. Consequently, at this time this report is unable to assert whether or not ETS exposure by itself is a risk factor for SIDS independent of smoking during pregnancy. Postnatal exposure may potentiate effects of in utero tobacco smoke exposure, or it may not have any additional effect.

Regarding an association of parental smoking with either upper respiratory tract infections (colds and sore throats) or acute middle ear infections in children, this report finds the evidence inconclusive.

1.2.1. ETS and Lung Cancer

The Surgeon General (U.S. DHHS, 1989) estimated that smoking was responsible for more than one of every six deaths in the United States and that it accounted for about 90% of the lung cancer deaths in males and about 80% in females in 1985. Smokers, however, are not the only

ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain many of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers. Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is biologically plausible.

Based on the firmly established causal association of lung cancer with active smoking with a dose-response relationship down to low doses (Chapter 4), passive smoking is considered likely to affect the lung similarly. The widespread presence of ETS in both home and workplace and its absorption by nonsmokers in the general population have been well documented by air sampling and by body measurement of biomarkers such as nicotine and cotinine (Chapter 3). This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This report addresses that question by reviewing and analyzing the evidence from 30 epidemiologic studies of effects from normally occurring environmental levels of ETS (Chapter 5). Because there is widespread exposure and it is difficult to construct a truly unexposed subgroup of the general population, these studies compare individuals with higher ETS exposure to those with lower exposures. Typically, female never-smokers who are married to a smoker are compared with female never-smokers who are married to a nonsmoker. Some studies also consider ETS exposure of other subjects (i.e., male never-smokers and long-term former smokers of either sex) and from other sources (e.g., workplace and home exposure during childhood), but these studies are fewer and represent fewer cases, and they are generally excluded from the analysis presented here. Use of the female never-smoker studies provides the largest, most homogeneous database for analysis to determine whether an ETS effect on lung cancer is present. This document assumes that the results for female never-smokers are generalizable to all nonsmokers.

Given that ETS exposures are at actual environmental levels and that the comparison groups are both exposed to appreciable background (i.e., nonspousal) ETS, any excess risk for lung cancer from exposure to spousal smoke would be expected to be small. Furthermore, the risk of lung cancer is relatively low in nonsmokers, and most studies have a small sample size, resulting in a very low statistical power (probability of detecting a real effect if it exists). Besides small sample size and low incremental exposures, other problems inherent in several of the studies may also limit their ability to detect a possible effect. Therefore, this document examines the data in several different ways. After downward adjustment of the relative risks for smoker

misclassification bias, the studies are individually assessed for strength of association and exposure-response trend. Then the study results are pooled by country using statistical techniques for combining data, including both positive and nonpositive results, to increase the ability to determine whether or not there is an association between ETS and lung cancer. Finally, in addition to the previous statistical analyses that weigh the studies only by size, regardless of design and conduct, the studies are qualitatively evaluated for potential confounding, bias, and likely utility to provide information about any lung carcinogenicity of ETS. Based on these qualitative considerations, the studies are categorized into one of four tiers and then statistically analyzed successively by tier.

Results from all of the analyses described above strongly support a causal association between lung cancer and ETS exposure. The overall proportion of individual studies found to show an association between lung cancer and ETS exposure is unlikely to occur by chance ($p < 0.005$). Similarly, the proportion showing a statistically significant dose-response trend ($p < 10^{-9}$) is highly supportive of a causal association. Combined results by country showed statistically significant associations for Greece (2 studies), Hong Kong (4 studies), Japan (5 studies), and the United States (11 studies), and in that order of strength of relative risk. Pooled results of the four Western European studies (three countries) actually showed a slightly stronger association than that of the United States, but it was not statistically significant, probably due to the smaller sample size. The combined results of the Chinese studies do not show an association between ETS and lung cancer; however, two of the four Chinese studies were designed mainly to determine the lung cancer effects of high levels of other indoor air pollutants indigenous to those areas, which would obscure a smaller ETS effect. These two Chinese studies do, however, provide very strong evidence on the lung carcinogenicity of these other indoor air pollutants, which contain many of the same components as ETS. When results are combined only for the other two Chinese studies, they demonstrate a statistically significant association for ETS and lung cancer.

The relative risks for Greece and Japan of 2.00 and 1.44, respectively, are probably the best estimates, because both female smoking prevalence and nontobacco-related lung cancer risks, which tend to dilute the estimates of ETS effects, are low in these two countries. Also, for the time period for which ETS exposure was of interest, spousal smoking is considered to be a better surrogate for ETS exposure in these societies than in Western countries, where other sources of ETS exposure (work, public places, and other nonhome environments) are generally higher.

Based on these analyses and following the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight-of-evidence, principally:

- Biological plausibility. ETS is taken up by the lungs, and components are distributed throughout the body. The presence of the same carcinogens in ETS and mainstream smoke, along with the established causal relationship between lung cancer and active smoking with the dose-response relationships exhibited down to low doses, make it reasonable to conclude that ETS is also a lung carcinogen.
- Supporting evidence from animal bioassays and genotoxicity experiments. The carcinogenicity of tobacco smoke has been established in lifetime inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of ETS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments. Positive results of genotoxicity testing for both MS and ETS provide corroborative evidence for their carcinogenic potential.
- Consistency of response. All 4 of the cohort studies and 20 of the 26 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Of the 17 studies judged to be of higher utility based on study design, execution, and analysis (Appendices A and C), 15 observed higher risks, and 6 of these increases were statistically significant, despite most having low statistical power. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.
- Broad-based evidence. These 26 case-control and 4 prospective studies provide data from 8 different countries, employ a wide variety of study designs and protocols, and are conducted by many different research teams. Results from all countries, with the possible exception of two areas of China where high levels of other indoor air lung carcinogens were present, show small to modest increases in lung cancer associated with spousal ETS exposure. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

- Upward trend in dose-response. Both the largest of the cohort studies, the Japanese study of Hirayama--200 lung cancer cases, and the largest of the case-control studies, the U.S. study by Fontham and associates (1991)--420 lung cancer cases and two sets of controls, demonstrate a strong dose-related statistical association between passive smoking and lung cancer. This upward trend is well supported by the preponderance of epidemiology studies. Of the total of 17 studies in which data are classified by exposure level, 11 were statistically significant for the trend despite most having low statistical power.
- Detectable association at environmental exposure levels. Within the population of married women who are lifelong nonsmokers, the excess lung cancer risk from exposure to their smoking husbands' ETS is large enough to be observed. Carcinogenic responses are usually detectable only in high-exposure circumstances, such as occupational settings, or in experimental animals receiving very high doses. In addition, effects are harder to observe when there is substantial background exposure in the comparison groups, as is the case here.
- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk for ETS exposure. The evidence remains statistically significant and conclusive, however, after adjustments for smoker misclassification. For the United States, the summary estimate of relative risk from nine case-control plus two cohort studies is 1.19 (90% confidence interval [C.I.] = 1.04-1.35) after adjustment for misclassification ($p < 0.05$). For Greece, 2.00 (1.42, 2.83), Hong Kong, 1.61 (1.25, 2.06) and Japan, 1.44 (1.13, 1.85), the estimated relative risks are higher than those of the United States and more highly significant after adjusting for the potential bias.
- Confounding cannot explain the association. The broad-based evidence for an association found by independent investigators across several countries, as well as the positive dose-response trends observed in most of the studies that analyzed for them, make any single confounder highly unlikely as an explanation for the results. In addition, this report examined potential confounding factors (history of lung disease, home heat sources, diet, occupation) and concluded that none of these factors could account for the observed association between lung cancer and ETS.

The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the widespread presence of ETS. Current smokers comprise approximately 26% of the U.S. adult population and consume more than one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to at least some ETS. As a biomarker of tobacco smoke uptake, cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported nonsmokers tested (50% equates to 63 million U.S. nonsmokers of age 18 or above).

The best estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers age 35 and over attributable to ETS (Chapter 6) is based on data pooled from all 11 U.S. epidemiologic studies of never-smoking women married to smoking spouses. Use of U.S. studies should increase the confidence in these estimates. Some mathematical modeling is required to adjust for expected bias from misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. Assumptions are also needed to relate responses in female never-smokers to those in male never-smokers and ex-smokers of both sexes, and to estimate the proportion of the nonsmoking population exposed to various levels of ETS. Overall, however, the assumptions necessary for estimating risk add far less uncertainty than other EPA quantitative assessments. This is because for ETS the extrapolation is based on a large database of human studies, all at levels actually expected to be encountered by much of the U.S. population.

The components of the 3,000 lung cancer deaths figure include approximately 1,500 female never-smokers, 500 male never-smokers, and 1,000 former smokers of both sexes. More females are estimated to be affected because there are more female than male nonsmokers. These component estimates have varying degrees of confidence; the estimate of 1,500 deaths for female never-smokers has the highest confidence because of the extensive database. The estimate of 500 for male never-smokers is less certain because it is based on the female never-smoker response and is thought to be low because males are generally subject to higher background ETS exposures than females. Adjustment for this higher background exposure would lead to higher risk estimates. The estimate of 1,000 lung cancer deaths for former smokers of both sexes is considered to have the lowest confidence, and the assumptions included are thought to make the estimate low as well.

Workplace ETS levels are generally comparable to home ETS levels, and studies using body cotinine measures as biomarkers demonstrate that nonhome exposures to ETS are often greater

than exposure from spousal smoking. Thus, this report presents an alternative breakdown of the estimated 3,000 ETS-attributable lung cancer deaths between spousal and nonhome exposures. By extension of the results from spousal smoking studies, coupled with biological measurements of exposure, more lung cancer deaths are estimated to be attributable to ETS from combined nonhome exposures - 2,200 of both sexes - than from spousal exposure - 800 of both sexes. This home-versus-other-sources partitioning depends on current exposure estimates that may or may not be applicable to the exposure period of interest. Thus, this breakdown contains this element of uncertainty in addition to those discussed above with respect to the previous breakdown.

Other estimates of annual U.S. nonsmoker lung cancer deaths attributable to ETS developed in this document give a range of 2,500 to 3,300. These other estimates use both mortality and cotinine exposure data from the largest and best-designed U.S. study (Fontham et al., 1991). Relatively small differences in cotinine ratios, as measures of exposure from spousal smoking, can result in substantial variability in population risk estimates. The range suggested above provides an estimation of the uncertainty in these estimates. Overall, however, considering the multitude, consistency, and quality of all these studies, the weight-of-evidence conclusion that ETS is a known human lung carcinogen, and the limited amount of extrapolation necessary, the confidence in the estimate of approximately 3,000 lung cancer deaths is medium to high.

1.2.2. ETS and Noncancer Respiratory Disorders

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly in infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. These cotinine concentrations were highly correlated with smoking (especially by the mother) in the child's presence. Nine million to twelve million American children under 5 years of age, or one-half to two-thirds of all children in this age group, may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986).

With regard to the noncancer respiratory effects of passive smoking, this report focuses on epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. DHHS) that bears on the potential association of parental smoking with detrimental respiratory effects in their children. These effects include symptoms of respiratory irritation (cough, sputum, or wheeze); acute diseases of the lower respiratory tract (pneumonia, bronchitis, and bronchiolitis); acute middle ear infections and indications of chronic middle ear infections (predominantly middle ear effusion); reduced lung function (from forced expiratory volume and flow-rate measurements);

incidence and prevalence of asthma and exacerbation of symptoms in asthmatics; and acute upper respiratory tract infections (colds and sore throats). The more than 50 recently published studies reviewed here essentially corroborate the previous conclusions of the NRC and Surgeon General regarding respiratory symptoms, respiratory illnesses, and pulmonary function, and they strengthen support for those conclusions by the additional weight-of-evidence (Chapter 7). For example, new data on middle ear effusion strengthen previous evidence to warrant the stronger conclusion in this report of a causal association with parental smoking. Furthermore, recent studies establish associations between parental smoking and increased incidence of childhood asthma. Additional research also supports the hypotheses that in utero exposure to mother's smoke and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization, changes that are known to predispose children to early respiratory illness. Early respiratory illness can lead to long-term pulmonary effects (reduced lung function and increased risk of chronic obstructive lung disease).

This document also summarizes the evidence for an association between parental smoking and SIDS, which was not addressed in the 1986 NRC or Surgeon General reports. SIDS is the most common cause of death in infants ages 1 month to 1 year. The cause (or causes) of SIDS is unknown; however, it is widely believed that some form of respiratory pathogenesis is generally involved. The current evidence strongly suggests that infants whose mothers smoke are at an increased risk of dying of SIDS, independent of other known risk factors for SIDS, including low birthweight and low gestational age, which are specifically associated with active smoking during pregnancy. However, available studies do not allow this report to conclude whether that increased risk is related to in utero versus postnatal exposure to tobacco smoke products, or to both.

The 1986 NRC and Surgeon General reports conclude that both the prevalence of respiratory symptoms of irritation and the incidence of lower respiratory tract infections are higher in children of smoking parents. In the 18 studies of respiratory symptoms subsequent to the 2 reports, increased symptoms (cough, phlegm, and wheezing) were observed in a range of ages from birth to midteens, particularly in infants and preschool children. In addition to the studies on symptoms of respiratory irritation, nine new studies have addressed the topic of parental smoking and acute lower respiratory tract illness in children, and eight have reported statistically significant associations. The cumulative evidence indicates strongly that parental smoking, especially the mother's, causes an increased incidence of respiratory illnesses from birth up to the first 18 months to 3 years of life, particularly for bronchitis, bronchiolitis, and

pneumonia. Overall, the evidence confirms the previous conclusions of the NRC and Surgeon General.

Recent studies also solidify the evidence for the conclusion of a causal association between parental smoking and increased middle ear effusion in young children. Middle ear effusion is the most common reason for hospitalization of young children for an operation.

At the time of the Surgeon General's report on passive smoking (U.S. DHHS, 1986), data were sufficient only to conclude that maternal smoking may influence the severity of asthma in children. The recent studies reviewed here strengthen and confirm these exacerbation effects. In addition, the new evidence is conclusive that ETS exposure increases the number of episodes of asthma in children who already have the disease. It is also suggestive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms, although the results are statistically significant only with children whose mothers smoke 10 or more cigarettes per day. While the evidence for new cases of asthma itself is not conclusive of a causal association, the consistent strong associations of ETS with both increased frequency and severity of the asthmatic symptoms and the established ETS effects on both the immune system and airway hyperresponsiveness lead to the conclusion that ETS is a risk factor for induction of asthma in previously asymptomatic children.

Regarding the effects of passive smoking on lung function in children, the 1986 Surgeon General and NRC reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Results from eight studies on ETS and lung function in children that have appeared since those reports add some additional confirmatory evidence suggesting a causal rather than an indirect relationship. For the population as a whole, the reductions are small relative to the interindividual variability of each lung function parameter. However, groups of particularly susceptible or heavily exposed subjects have shown larger decrements. The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. Exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

With respect to lung function effects in adults exposed to ETS, the 1986 NRC and Surgeon General reports found the data at that time inconclusive, due to high interindividual variability and the existence of a large number of other risk factors, but compatible with subtle deficits in lung function. Recent studies confirm the association of passive smoking with small reductions in lung function. Furthermore, new evidence also has emerged suggesting a subtle association between exposure to ETS and increased respiratory symptoms in adults.

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

In reviewing the available evidence indicating an association (or lack thereof) between ETS exposure and the different noncancer respiratory disorders analyzed in this report, the possible role of several potential confounding factors was considered. These include other indoor air pollutants; socioeconomic status; effect of parental symptoms; and characteristics of the exposed child, such as low birthweight or active smoking. No single or combined confounding factors can explain the observed respiratory effects of passive smoking in children.

For diseases for which ETS has been either causally associated (lower respiratory tract infections) or indicated as a risk factor (asthma cases in previously asymptomatic children), estimates of population attributable risk can be calculated. A population risk assessment (Chapter 8) provides a probable range of estimates that 8,000 to 26,000 cases of childhood asthma per year are attributable to ETS exposure from mothers who smoke 10 or more cigarettes per day. The confidence in this range of estimates is medium and is dependent on the suggestive evidence of the database. While the data show an effect only for children of these heavily smoking mothers, additional cases due to lesser ETS exposure are also a possibility. If the effect of this lesser exposure is considered, the range of estimates of new cases presented above increases to 13,000 to 60,000. Furthermore, this report estimates that the additional public health impact of ETS on asthmatic children includes over 200,000 children whose symptoms are significantly aggravated and as many as 1,000,000 children who are affected to some degree.

This report estimates that ETS exposure contributes 150,000 to 300,000 cases annually of lower respiratory tract illness in infants and children younger than 18 months of age and that 7,500 to 15,000 of these will require hospitalization. The strong evidence linking ETS exposure to increased incidence of bronchitis, bronchiolitis, and pneumonia in young children gives these

estimates a high degree of confidence. There is also evidence suggesting a smaller ETS effect on children between ages 18 months and 3 years, but no additional estimates have been computed for this age group. Whether or not these illnesses result in death has not been addressed here.

In the United States, more than 5,000 infants die of SIDS annually. It is the major cause of death in infants between the ages of 1 month and 1 year and the linkage with maternal smoking is well established. The Surgeon General and World Health Organization estimate that more than 700 U.S. infant deaths per year from SIDS are attributable to maternal smoking (U.S. CDC, 1991a). However, this report concludes that at present there is not enough direct evidence supporting the contribution of ETS exposure to declare it a risk factor or to estimate its population impact on SIDS.

U.S. Environmental Protection Agency
Science Advisory Board
Indoor Air Quality and Total Human Exposure Committee
Open Meeting
July 21-22, 1992

Pursuant to the Federal Advisory Committee Act, P.L. 92-463, notice is hereby given that the Science Advisory Board's (SAB) Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) (hereafter, the Committee) will meet on July 21-22, 1992 in the Main Ballroom of the Holiday Inn, 15th Street and Jefferson Davis Highway, Arlington, VA 22202. The meeting will begin on both days at 9:00 a.m., and end no later than 5:00 p.m. on July 22. The meeting is open to the public and seating is on a first-come basis.

BACKGROUND

The purpose of the meeting is for the Committee to review the U.S. Environmental Protection Agency's (EPA) draft report *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (EPA/600/6-90/006B)*. This document was prepared by the Agency's Human Health Assessment Group, Office of Research and Development (ORD), at the request of the Agency's Indoor Air Division, Office of Air and Radiation (OAR), under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants. This report is a revision of an earlier report titled, *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children (EPA/600/6-90/006A)*, which the SAB reviewed in public session on December 4-5, 1990. As a result of that review, the SAB suggested several areas in which the health risk assessment could be improved, and offered to provide additional advice on a revised document (See the SAB's report issued as a result of that review: *An SAB Report: Review of Draft Environmental Tobacco Smoke Health Effects Document, EPA-SAB-IAQC-91-007, April 1991)*. The Agency has now completed its revision of the document and has requested that the SAB review the revised draft.

CHARGE TO THE COMMITTEE

As part of the tentative Charge to the Committee, the Agency has requested that the SAB answer the following questions (Chapter numbers refer to the revised draft EPA document, EPA/600/6-90/006B):

I - ETS EXPOSURE (Chapter 3)

1) Do the conclusions on the chemical similarities of ETS and mainstream smoke warrant the toxicological comparison between passive and active smoking made as part of the biological plausibility arguments for lung cancer (Chapter 4) and non-cancer respiratory disorders (Chapter 7)?

2) Is the extent of ETS exposure in various environments adequately characterized?

3) Are the methods of assessing ETS exposure and the uncertainties associated with each accurately described?

II - LUNG CANCER

A. HAZARD IDENTIFICATION (Chapters 4 and 5)

4) Is the evidence for the lung carcinogenicity of ETS presented adequately?

5) Does any of the new information alter the SAB conclusion regarding the categorization of ETS as an EPA Group A carcinogen?

B. POPULATION IMPACT (Chapter 6)

6) Is the approach used to derive estimates of U.S. female never-smoker lung cancer risk scientifically defensible?

7) Is the approach used to extrapolate lung cancer risk from female never-smokers to male never-smokers and former smoker of both sexes scientifically defensible?

8) Are the assumptions used to derive these lung cancer population estimates and the uncertainties involved characterized adequately?

9) Is the degree of confidence in these estimates as stated appropriately characterized?

III - NONCANCER RESPIRATORY DISORDERS

A. HAZARD IDENTIFICATION (Chapter 7; Sections 8.1 and 8.2)

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10) Have the biological plausibility arguments been adequately presented?

11) Have the most important confounders been properly addressed?

12) Has the weight of evidence been properly characterized? Are the conclusions scientifically defensible?

13) Is the evidence with respect to maternal smoking and sudden infant death syndrome properly characterized? Should this evidence be included in this report?

B. POPULATION IMPACT (Chapter 8)

14) Is the presented population impact of ETS on lower respiratory infections and asthma in children scientifically defensible?

15) Are the assumptions, uncertainties, and degree of confidence in the ranges of population impact estimates adequately characterized?

This Charge is subject to change and the Committee may elect to investigate other areas as well.

AVAILABILITY OF DOCUMENTS AND INFORMATION

1) The present EPA draft document (*Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (EPA/600/6-90/006B)*) will be made available to the interested public and the Committee on or about June 22, 1992. Copies of this draft document are not available from the Science Advisory Board. Single copies may be obtained from the following source(s):

a) Center for Environmental Research Information (CERI-FRN), U.S. Environmental Protection Agency, 26 W. Martin Luther King Drive, Cincinnati, OH 45268; telephone: (513) 569-7562; FAX: (513) 569-7566. Please provide the document number (EPA/600/6-90/006B), and your name and mailing address. Availability may be limited.

b) National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161; telephone: (703) 487-4650. Availability date may vary, please check with NTIS. The NTIS ordering number is PB92-182344. (cost $59.00 paper; $19.00 microfiche).

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c) The revised draft document will also be available for inspection at the ORD Public Information Shelf, U.S. EPA Headquarters Library, 401 M Street, S.W., Washington, DC 20460; the EPA Regional Libraries; and the Federal Depository Libraries.

2) The earlier EPA draft document (*Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children (EPA/600/6-90/006A)*) is available only from the following source: National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161; telephone: (703) 487-4650. The NTIS ordering number is PB90-261-652/AS. (cost $35.00 paper; $12.50 microfiche). This document was reviewed earlier by the SAB and is not a subject of the present review.

3) The Science Advisory Board report: *Review of Draft Environmental Tobacco Smoke Health Effects Document (EPA-SAB-IAQC-91-007) April 1991*, is available in single copies only from: U.S. EPA, Science Advisory Board (A-101), Office of the Staff Director, ATTN: Ms. Lori Gross, 401 M Street, SW, Washington, DC 20460 (street and mailing address are the same); telephone: (202) 260-4126 and FAX: (202) 260-9232. Please provide the report title, SAB report number and your name and mailing address to obtain a copy.

4) For further information concerning the meeting including a draft agenda, or to reserve speaking time on the agenda (see below), please contact Mr. Robert Flaak, Assistant Staff Director, (mailing address: Science Advisory Board Staff Office (A-101F), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460; street address: Suite 508, 499 South Capitol Street, Washington, DC 20460), telephone: (202) 260-6552 and FAX: (202) 260-7118. COPIES OF THE EPA DRAFT DOCUMENTS AND THE SAB REPORT ARE NOT AVAILABLE FROM THE SAB STAFF OFFICE.

PROCEDURES FOR PROVIDING COMMENTS

The Agency is not soliciting public comment on its draft document. However, as a procedural matter, the Science Advisory Board normally accepts either written or oral comment on issues that are under its review. To be most useful, the comments should be focused on the particular issues before the Committee, as summarized in the Charge to the Committee above. Comments submitted to the SAB will be provided to the Committee for

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consideration during the review process. The SAB does not acknowledge receipt of nor does it provide a response to any public comments received.

1) Oral Comment: Oral comment is taken during a specified period during the public meeting (this will be announced in the agenda). Members of the public who wish to make a brief oral presentation to the Committee must contact Mr. Flaak in writing (via letter or FAX) no later than 4:00 p.m. (eastern time) on July 14, 1992 in order to reserve time on the Agenda. The request must include the name of the person making the presentation, organizational affiliation represented, a summary of the issue to be discussed (cf., the Charge to the Committee above), and identification of any audio-visual requirements. Phone calls are welcome to clarify the process, however, a reservation to speak must still be made in writing. The SAB expects that public statements presented at its meetings will not be repetitive of previously submitted oral or written statements. In general, each individual or group making an oral presentation will be limited to a total time of five minutes. A copy of the text and copies of any visuals used must be provided to Mr. Flaak at the time of the presentation, and will be made part of the public record.

2) Written Comment: Written statements of any length may be provided to the Committee up until the meeting. Copies of these statements received in the SAB Staff office by noon (eastern time) on July 6, 1992 will be mailed to the Committee before the meeting; copies received after that date will be provided to the Committee at the meeting. Members of the public who submit written comments either before or at the meeting are requested to provide at least 50 copies of any such documents to Mr. Flaak to allow for adequate distribution of their position or information. Copies of all comments provided to the SAB as a result of this review will be made part of the public record and will also be provided to the Agency for their information.

June 12, 1992
Date

Donald G. Barnes
Dr. Donald Barnes
Staff Director
Science Advisory Board

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APPENDIX C

BACKGROUND MATERIALS REGARDING THE U.S. ENVIRONMENTAL PROTECTION AGENCY'S REVISED RISK ASSESSMENT

TOPICS INCLUDED IN BACKGROUND INFORMATION

* General Comments Prior to a Thorough Review of the Revised Draft Risk Assessment
* General Comments re: Interpreting Epidemiologic Studies
* General Discussion: ETS and the Alleged Association with Lung Cancer
* General Discussion re: Parental Smoking
* Historical Reference: ETS Documents and the Environmental Protection Agency (EPA)
* Summary of Industry Responses to the June 1990 First Draft Risk Assessment

GENERAL COMMENTS PRIOR TO
THOROUGH REVIEW OF THE
REVISED DRAFT RISK ASSESSMENT

While we have not had an opportunity to review the revised draft, it is important to understand that it -- and any conclusions that it makes -- remain draft, subject to review again by outside experts and the EPA's SAB.

What we do know at this juncture is that many organizations and individuals, including the tobacco industry, have raised serious concerns over a tendency at EPA to place policy ahead of science.

- In March 1992, an Expert Panel convened by EPA's Administrator issued a report on the Agency's use of science. The report, Safeguarding the Future: Credible Science, Credible Evidence, admonished EPA that "science should never be adjusted to fit policy," noting the widespread perception that such adjustments are routinely performed at EPA to fit political and personal agendas.

- Credible Science also concluded that "[c]urrently, EPA science is of uneven quality, and the Agency's policies and regulations are frequently perceived as lacking a strong scientific foundation."

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Further, EPA's Guidelines for assessing carcinogenic risk require sufficient human evidence in support of designation of a Group A carcinogen. The guidelines do not permit a human carcinogen classification based on weak and inconsistent epidemiologic data or on an assumed similarity between two different compounds.

- The original review in 1990 by the EPA's SAB concluded that the lung cancer issue could not be resolved based solely on the weak and inconsistent epidemiologic data. The SAB then took the extraordinary step of urging EPA staff to attempt to "make the case" against ETS based on data concerning active smoking -- apparently on the faulty premise that ETS is simply a diluted form of the mainstream smoke inhaled by the smoker.

  The National Academy of Sciences (1986) and other experts have concluded, however, that there are significant differences between mainstream smoke and ETS. The differences in chemical composition, physical properties and concentration have been well noted.

A revised draft risk assessment that continues to designate ETS as a Group A carcinogen demonstrates that EPA has chosen to ignore the troubling conclusions of Credible Science and

the Expert Panel's recommendations for reform. Once again, it appears EPA has chosen to "adjust science to fit the policy."

General Comments re: Interpreting Epidemiologic Studies

The initial draft ETS risk assessment by the EPA (June 1990) was the first risk assessment ever conducted by EPA that ~~is~~ was based entirely on epidemiologic evidence.

Epidemiology is an observational science concerned with the search for associations between agents and disease through organized collection and analysis of data about the human population. ETS epidemiologic studies involve the comparison of lung cancer risk between nonsmokers married to nonsmokers (therefore presumed not to be exposed to ETS) and nonsmokers married to smokers (presumed to be exposed to ETS).

Given the errors inherent in epidemiologic studies--including the ETS studies -- a rigorous set of criteria must be met to support a judgment of cause and effect from a set of epidemiologic data. These include:

1. Strength of Association: The stronger the risk observed, the more likely that the agent is actually causing the effect. Relative risks less than 2.0 are considered difficult to attribute to the agent in question rather than to flaws in study design and execution.

2. Consistency of Association: Consistent results across studies are considered evidence that the association may be causal.

3. Replication: The association should be replicated in different circumstances, places and times.

4. Dose-Response Relationship: Differential exposure levels should produce differential results. That is, higher dosage should produce a more pronounced result.

5. Temporal Relationship: The effect should reflect sufficient duration and timing of exposure.

6. Biological Plausibility: The effect should make sense biologically based on what is known about the agent.

In order to infer causation, the epidemiologic evidence must also be supported by evidence from other disciplines, such as pharmacology and toxicology (e.g., animal studies, understanding of biological mechanisms).

Application of these criteria demonstrates that the spousal smoking studies relied upon by the EPA do not convincingly support conclusion that ETS is a cause of lung cancer in nonsmokers.

A review of the published ETS-lung cancer studies reveals the following:

1. A total of 27 case-control and 3 cohort studies of spousal smoking and nonsmoker lung cancer are available in the published literature. Of those, only six have reported a statistically significant association; twenty four do not achieve statistical significance. The 24 studies therefore are consistent with the null hypothesis of no association between spousal smoking and lung cancer in nonsmokers.

2. One of the most recent ETS lung cancer studies published in the scientific literature -- a large case-control study of a population of Chinese women -- reported no association between ETS and lung cancer. In fact, the study reported a statistically significant inverse relationship between spousal smoking and lung cancer risk.

3. Even the few studies that have reported statistically significant associations between spousal smoking and lung cancer report risk ratios that are weak at best -- all well below 3.0. Epidemiologists agree that studies reporting such weak associations are difficult to interpret because of the problems inherent in the design and conduct of observational studies.

4. Despite the fact that the risk assessment is used to form the basis for EPA's smoking policy recommendations for the workplace, only 12 existing ETS studies have even attempted to examine workplace exposure to ETS. Of those 12, only <u>two</u> reported a statistically significant association.

5. All of the existing epidemiologic studies of ETS and lung cancer -- and particularly the Hirayama study, which carries great weight in meta analyses of the ETS database -- reflect a number of flaws which complicate their interpretation. These include:

a. Inadequate Exposure Classification: Because ETS epidemiology is based on reports of spousal smoking habits, existence or degree of actual nonsmoker exposure to ETS is unknown.

b. Inadequate Attention to Confounding Factors: Confounding factors are lifestyle or any other characteristics that are common to both the agent and the disease under study and which therefore could create an apparent association where none in fact exists. In the case of ETS, a confounding factor is one which is common to marriage to a smoker and to lung cancer. Diet is one example: if smokers tend to have poorer diets than nonsmokers, if a nonsmoker married to a smoker may be expected to share the poorer diet, and if diet is associated with lung cancer, than an effect attributed to ETS may in fact be due to diet. Other potential confounding factors include alcohol consumption, occupational exposures and socio-economic status.

Reliance on spousal smoking as the index of exposure in ETS studies, instead of direct,

objective measures, increases the likelihood that factors common to both lung cancer risk and marriage to a smoker confound the apparent ETS-lung cancer association. Virtually none of the ETS-lung cancer studies which report an association have adequately controlled for the appropriate confounding factors.

c. Inadequate Consideration of Miscellaneous Bias: Most of the ETS studies have failed to consider the effects of misclassification bias, which occurs when a study participant reports his smoking status falsely -- that is, when a true nonsmoker claims to be a smoker or a true smoker claims to be a nonsmoker. Misclassification bias is particularly likely in the ETS epidemiology, since the studies rely on self reports of smoking status with no independent verification.

In ETS studies, misclassification bias is thought to occur more frequently in the population classified as exposed, for two major reasons. First, smokers are more likely to claim to be nonsmokers than are nonsmokers to

claim to be smokers. Second, smokers tend to marry smokers and nonsmokers to marry nonsmokers.

It is therefore likely that at least some professed nonsmokers married to smokers and therefore classified as ETS-exposed are in fact current or former smokers. Because the bias is systematic, occurring more frequently in exposed than non-exposed groups, it could tend to produce an artificially high relative risk.

d. Questionable Ascertainment of Causes of Death: The largest ETS studies rely on death certificates rather than histopathological diagnoses to determine the cause of death, increasing the likelihood of misdiagnosis or that cancers identified as primary to the lung may actually have originated elsewhere.

e. Inadequate Consideration of Other Biases: These include recall bias, produced by reliance on family members of more distant relatives

for information on spousal smoking habits; selection bias; interviewer bias and others.

GENERAL DISCUSSION
ETS AND ALLEGED
ASSOCIATION WITH LUNG CANCER

It has been argued that environmental tobacco smoke (ETS) exposure increases the risk of lung cancer in nonsmokers.[1,2] This claim is based upon data from epidemiologic studies of women who report spousal smoking in the home. The studies cited in support of the claimed association between spousal smoking and lung cancer have been heavily criticized in the scientific literature. For example, of the 30 published epidemiologic studies examining the issue of spousal smoking and lung cancer in nonsmokers, none actually measured exposure to ETS. Also, the risk estimates reported in the studies are "weak" in epidemiologic terms (i.e., less than 3.0). Twenty-four of the 30 studies do not achieve statistical significance; that is, their conclusions are consistent with the null hypothesis of no association. In fact, nine of the spousal smoking studies report risk estimates that are negative (i.e., less than 1.0); one of these is statistically significant.

Studies on spousal smoking are of questionable relevance to the workplace. To date, 12 of the 30 published epidemiologic studies on the issue of spousal smoking and lung cancer in nonsmokers have assessed reported workplace exposures to ETS. Ten of the 12 studies report associations between ETS and nonsmoker lung cancer which do not achieve statistical significance; only two studies report marginally statistically significant increased risks for persons who reported exposure to ETS in the workplace.

Thus, the existing data examining reported workplace ETS exposures and lung cancer incidence in nonsmokers are consistent with the null hypothesis of no association.

Bias and Confounding Factors in Studies on Spousal Smoking

The epidemiologic studies on spousal smoking and lung cancer[3-32] have been criticized for their failure to account for a variety of biases and confounding factors that could affect the validity of their reported findings. In their discussion of such studies, for example, American researchers Ernst Wynder and Geoffrey Kabat cautioned that "if the observed relative risk is small," which they note is "the case" in the reported associations between spousal smoking and lung cancer, "it is important to determine whether the effect could be due to biased selection of subjects, confounding, biased reporting, or anomalies of particular subgroups."[33]

Misclassification of exposure may contribute to the reported increase in lung cancer risks among nonsmokers, according to several scientists. For example, none of the studies on ETS and lung cancer provides direct observational information on ETS exposures. Instead, spouses, next-of-kin or friends were asked to estimate the amount of ETS to which they thought the subject was exposed. Such estimates may result in what is called exposure

misclassification, which several researchers have reported leads to improper indices of exposure and incorrect estimations of risk.[4,34-39] In Garfinkel's study, for example, the reported risk for lung cancer in the women exposed to ETS was actually less than for women not exposed when either the women's or their husbands' estimates were used.[4] Other authors, including the National Research Council, have recently criticized questionnaires used in ETS studies for not being standardized or validated; they pointed out that misclassification of exposure may occur if the questionnaire is not appropriately designed.[40-42]

Biostatistician S. James Kilpatrick has identified another form of misclassification, called differential misclassification, which results "from the tendency of respondents to inflate the amount of ETS exposure for lung cancer cases and deflate the report of exposure for controls."[34] Similarly, Dr. Ernst Wynder, President of the American Health Foundation, notes that "relatives of a nonsmoking lung cancer patient are more likely to report passive inhalation exposure on the part of their relative than are relatives of a control patient."[43] Wynder and a co-author also noted that even if the patient herself is interviewed, some overreporting of ETS exposure may occur.[44]

Misclassification of case studies can also arise if diagnoses of lung cancer are not histologically confirmed.[45]

Without histologic confirmation, a tumor arising at another site and metastasizing or traveling to the lung could be erroneously identified as a primary lung tumor.

A more subtle form of potential bias, known as "publication bias," stems from the apparent unwillingness of scientific and medical journals to publish studies which report negative or weakly positive results.[46-48] Scientists have recently expressed concern over the growing trend among such journals to overemphasize (and hence to publish) only those studies which report positive increases in risk.[49,50] Published studies which are combined for meta-analyses, therefore, may not truly represent all investigations on the issue of ETS exposure and lung cancer.[51]

Statistician and epidemiologist Peter Lee has argued that the increased risks reported in the various studies are the result of an inherent bias in study design rather than the result of any genuine effect from exposure to ETS.[52-59] In his analyses, Lee has presented data which indicate that the reported risks cannot be explained on the basis of either ETS exposure or dose for the nonsmoker. Rather, he contends that the reported "risks" are the result of bias caused by a small number of smokers who are misclassified in the studies as nonsmokers.

Moreover, most of the epidemiological studies on ETS and lung cancer have failed to consider age differences, diet, occupation and exposures to indoor or outdoor pollution as potential confounding elements. The importance of such factors is increasingly underscored in more recent publications.[60,61]

In developing countries, for example, the use of kerosene, gas, coal, liquefied petroleum gas, straw or wood for heating and cooking reportedly contributes to elevated levels of certain indoor air constituents, and may lead to increases in disease incidence.[62,63] Early, limited reports first suggested that exposures to indoor air constituents may be responsible for the increased risk of lung cancer among Oriental women.[64,65] Since then, a number of studies have reported elevated risks for lung cancer associated with the use of coal in stoves and other indigenous heating devices in China.[14,29,32,66-72] At least two papers have reported that certain cooking techniques which produce oil vapors, e.g., stir-frying and deep frying, were associated with increased lung cancer risks among Chinese women.[14,25] Another paper reported that limits on national air quality standards were consistently exceeded in the Chinese kitchens studied.[73] Similarly, the use of kerosene, coal, wood or straw has been associated with an increased risk of lung cancer in Japanese women.[27,30] It appears that poor indoor air quality may not be restricted to Asian countries; similar observations regarding workplaces and offices

have been made in Greece as well.[74]

In addition to poor indoor air quality from heating and cooking fuels, at least one epidemiologic study from northeast China reported statistically significant associations between outdoor air pollution and lung cancer incidence.[72]

Several aspects of diet have been suggested to be possible confounding factors. For instance, Dr. Linda Koo, in several papers published between 1988 and 1990, re-analyzed her data on nonsmoking wives of smokers.[75-78] Her results indicated that wives of nonsmoking husbands had "healthier" lifestyles than wives of smoking husbands; they exhibited higher socio-economic status and had better indices of family cohesiveness and lower frequencies of selected health problems and complaints. An important and statistically significant difference was reportedly found in the diets of the two groups. Wives of smoking husbands consumed more processed and spicy foods and ate fewer fresh fruits and vegetables than wives of nonsmoking men. Koo concluded that such correlates of smoking status "act as important confounders when evaluating health risks among families with smoking husbands." She also wrote:

> [C]aution should be exercised when interpreting data on ETS. It may not be the hazards of tobacco smoke that are being evaluated, but a whole range of behaviors that result from having a smoking husband, which may in turn increase the risk for certain diseases among their wives

and children.[75]

Moreover, in 1989, Sidney and colleagues reported that nonsmokers living with smokers consumed less carotene (Vitamin A) than nonsmokers who lived with other nonsmokers. They concluded that "dietary beta-carotene intake is a potential confounder and should be measured whenever possible in studies of the relation between passive smoking and lung cancer."[79] In 1991, additional supportive data were provided by Le Marchand and colleagues' study of women in Hawaii, which found that beta-carotene intake was inversely associated with ETS exposure.[80] The authors noted: "Decreased beta-carotene consumption could explain, in part or in total, the moderately elevated lung-cancer risk observed for passive smokers in past studies." In addition, in a 1990 abstract, Waller and Smith reported a correlation between serum beta-carotene level and socioeconomic status, suggesting that the relationship may be even more complex.[81] Another aspect of diet, namely, consumption of green tea, was associated with a statistically significant increased risk of lung cancer in women in Hong Kong.[82] Similar results were first reported at a 1987 conference in Tokyo, in a paper calling for increased attention to possible relationships between substances taken in orally and lung cancer.[83]

Other potential confounders in studies of ETS and lung cancer include occupational exposures;[13,14,29,80,84] personal

health factors (e.g., menstrual cycle length, history of respiratory disease);[14,29,32,78] family history of lung cancer;[29,55] and even keeping pet birds.[85] More than 20 independent risk factors for lung cancer were listed in a recent article by Gori and Mantel.[86] These authors pointed out that:

> Since many of the RRs [for those risk factors] are substantially larger than any reported for the association of lung cancer and ETS, even weak contributions by combinations of these confounders would be cumulative and could be more than sufficient to explain the marginal lung cancer risks that some epidemiologic studies of ETS have reported. In fact it is likely to be so, because these studies have not controlled for the factors in any meaningful or comprehensive way, while other investigations provide evidence that several of those risk factors cluster and selectively segregate in families with smokers.

Swedish scientist Ragnar Rylander summed up the importance of confounders in a 1990 article.[61] He cautioned that studies evaluating the relationship between exposure to ETS and lung cancer "must take into account other environmental risk or protection factors and the possibility that exposure to environmental tobacco smoke may be confounded," which he noted "has not been considered in the majority of such studies." He concluded: "Until this has been done, the claim of causality between environmental tobacco smoke and lung cancer remains uncertain."

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GENERAL
DISCUSSION RE: PARENTAL SMOKING

One of the most emotional claims regarding ETS is that parents may increase their children's risk of respiratory disease by smoking at home. While some studies have reported an association between parental smoking and respiratory symptoms and disease in children, others have not.

The studies reporting such associations invariably fail to consider other important factors that are associated with respiratory disease in children. These include dampness in the home, the existence of contagious respiratory infections at home and in day-care facilities, poor nutrition, proximity of the home in relation to industry and outdoor pollution, and heredity. These factors, called confounders, have been associated with childhood respiratory conditions independent of whether or not the parents smoke, according to reports in the scientific literature. A U.S. government report on parental smoking studies examined the issue of such confounding factors and cautioned that "any study which ignores them will be seriously flawed." (United States Department of Health and Human Services, Public Health Service, National Institutes of Health, Report of Workshop on Respiratory Effects of Involuntary Smoke Exposure: Epidemiologic Studies, May 1-3, 1983.)

The published studies on parental smoking, which employ different data collection methods and analyses, tend to yield

factually incompatible and contrary conclusions. Many of the studies are poorly designed and executed. None of them actually measure ETS exposure but instead rely on recall about exposures through respondent answers to questionnaires. It has been reported that even "slight changes" in the way the questions are phrased and in who answers the questionnaire can make substantial differences in the types of responses obtained. (Ekwo, E., Weinberger, M.M., Lachenbruch, P.A. and Huntley, W.H., "Relationship of Parental Smoking and Gas Cooking to Respiratory Disease in Children," Chest 84(6): 662-668, 1983; and Schenker, M., Samet, J.M. and Speizer, F.E., "Risk Factors for Childhood Respiratory Disease: The Effect of Host Factors and Home Environmental Exposures," American Review of Respiratory Disease 128: 1038-1043, 1983.) Another researcher who is critical of parental smoking has conceded that "quantitative assessment of involuntary exposure of infants and children to ETS has been very imprecise and probably inaccurate." (Tager, I.B., "Health Effects of 'Passive Smoking' In Children," Chest 96(5): 1161-1164, 1989.)

In 1988, two U.S. investigators examined 30 of the major parental smoking studies and evaluated them for their scientific validity. They noted that while several studies of adequate scientific design reported an association between reported parental smoking and childhood respiratory conditions, "most studies had significant design problems that prevent reliance on their

conclusions." The authors concluded that "many questions remain, and future studies should consider important methodological standards to determine more accurately the effect of passive smoking on child health." (Rubin, D. and Damus, K., "The Relationship Between Passive Smoking and Child Health: Methodologic Criteria Applied to Prior Studies," Yale Journal of Biological Medicine 61(5): 401-411, 1988.) Claims regarding parental smoking and specific respiratory conditions are discussed below.

Asthma

In 1990, German researchers reported that exposing children with bronchial asthma to even high levels of ETS for one hour did not affect their lung function or bronchial responsiveness. (Oldigs, M., Jorres, R., and Magnussen, H., "Acute Effect of Passive Smoking on Lung Function and Airway Responsiveness in Asthmatic Children," Joint Meeting SEP-SEPCR, London, Barbican Centre, September, 1990.) A 1992 review of the epidemiological literature on ETS exposure and respiratory health in children reported that only 5 of the 21 major studies on asthma in children report a statistically significant association between parental smoking and asthma in the school-age children of smoking parents. (Hood, R.D., Wu, J.M., Witorsch, R. and Witorsch, P., "Environmental Tobacco Smoke Exposure and Respiratory Health in Children: An Updated

Critical Review and Analysis of the Epidemiological Literature," Indoor Environment 1: 19-35, 1992.)

Lung Function

In 1982, a United States research group showed that a comparison of body size with lung function eliminated any reported correlation between parental smoking and children's lung function. (Lebowitz, M., Armet, D.B., and Knudson, R., "The Effect of Passive Smoking on Pulmonary Performance in Children," Environment International 8: 371-373, 1982.) The magnitude of pulmonary function changes reportedly associated with parental smoking are so small that researchers are unsure of any clinical significance of the reported decrements. For example, after reviewing the literature on parental smoking and pulmonary function in children, researchers in 1992 asserted that the reported decrements in pulmonary function were, "with few exceptions," small and that all of the values were still within the normal range. (Hood, R.D., Wu, J.M., Witorsch, R. and Witorsch, P., "Environmental Tobacco Smoke Exposure and Respiratory Health in Children: An Updated Critical Review and Analysis of the Epidemiologic Literature," Indoor Environment 1: 19-35, 1992.)

Otitis Media (Middle Ear Disease)

A group of Dutch researchers has asserted that "there is little evidence that parental smoking has an effect on the risk for OME," and noted that "the literature is not consistent." (Ziehlhuis, G.A., Heuvelmans-Heinen, E.W., Rach, G.H., and Van Den Broek, P., "Environmental Risk Factors for Otitis Media with Effusion in Preschool Children," Scandinavian Journal of Primary Health Care 7(1): 33-38, 1989.) A 1992 review of the epidemiological literature on ETS exposure and respiratory health in children reported that only 6 of the 17 major studies on otitis media have reported a statistically significant association between parental smoking and the incidence of otitis media in children. (Hood, R.D., Wu, J.M., Witorsch, R. and Witorsch, P., "Environmental Tobacco Smoke Exposure and Respiratory Health in Children: An Updated Critical Review and Analysis of the Epidemiological Literature," Indoor Environment 1: 19-35, 1992.)

Infant Birthweight

A 1990 study noted that, after adjusting for 57 different confounding factors, parental smoking had no statistically significant effect on infant birthweight. (Rantakallio, P., Hartikainen-Sorri, A.L. and Leino, T., "The Effect of Parental Smoking and Industrial Pollution on Birth Weight." In: Indoor

Air Quality. H. Kasuga (ed.). Berlin, Heidelberg, Springer-Verlag, 219-225, 1990.)

Sudden Infant Death Syndrome (SIDS)

The term "crib death" refers to the sudden infant death syndrome (SIDS), which has been defined as the sudden death of any infant or young child, unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death. This definition clearly suggests just how little is really known about this condition. Indeed, John L. Emery, Emeritus Professor of Pediatric Pathology at the University of Sheffield, in a November 1989 editorial in the British Medical Journal observed:

> Questions are now beginning to be asked, including: Is there such an entity as the sudden infant death syndrome or is it a convenient diagnostic dustbin? (p. 1240)

Similarly, a September 1989 article in the Journal of the American Medical Association observed:

> A syndrome of apparently healthy infants dying suddenly and inexplicably was described almost a century ago and has been the subject of systematic study for more than 40 years. But understanding of crucial aspects of sudden infant death syndrome (SIDS) -- what causes it, what infants are at risk, and how to prevent it -- is still limited. (p. 1565)

HISTORICAL REFERENCE: ETS DOCUMENTS AND THE ENVIRONMENTAL PROTECTION AGENCY (EPA)

Three documents concerning ETS have originated with the EPA. They are:

ETS Draft Risk Assessment: This document addresses health risks reportedly associated with ETS and advocates classification of ETS as Group A ("known human") carcinogen.

Workplace Smoking Policy Guide: This document addresses health issues in the workplace, including ETS and recommends policy concerning ETS, although at the time of issuance the scientific basis of the risk assessment, on which the guide is primarily based, had not yet been reviewed or finalized.

ETS Compendium of Technical Information: This document containing eleven chapters was drafted by various EPA contractors. It was originally designed to provide a technical basis for the Workplace Policy Guide. The EPA, however, now states that the Compendium is not an "official" EPA document.

Chronology of Prior Events at the EPA

June 25, 1990 — EPA released: (1) Draft Risk Assessment on ETS; (2) Draft Workplace Smoking Policy Guide; (3) Notice of EPA Public Comment Period and

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indication of referral to Scientific Advisory Board (SAB).

October 1, 1990 — Public comment period for Risk Assessment and Policy Guide ended. Over 100 comments on each document were submitted.

November 1, 1990 — The Offices of Research and Development and Air and Radiation requested that the Scientific Advisory Board (SAB) review the two documents. [The SAB's review of the Workplace Guide was limited to approximately 20 pages which dealt with scientific issues.]

November 20, 1990 — Notice of public meetings to be held December 4 and 5 published in the Federal Register.

December 4, 1990 — SAB conducted a public meeting in Arlington, Virginia, which focused primarily on the ETS Draft Risk Assessment but with some discussion of the Draft Workplace Smoking Policy Guide. Dr. Morton Lippmann, Chairman of the EPA's Scientific Advisory Board on Indoor Air Quality and Total Human Exposure Committee presided. Public comments were received.

December 5, 1990 — On the second day of the SAB meeting, the Committee reviewed the documents. After the meeting, Chairman Lippmann held a press conference to answer questions. He stated that he was speaking for himself, not the SAB, the EPA or other SAB members. At the press conference he stated: (1) there is enough evidence to classify ETS as a "Group A" carcinogen; and (2) there is even stronger evidence that ETS is associated with respiratory effects in children than the Draft Risk Assessment had reported.

April 18, 1991 — The Executive Committee of the EPA's Scientific Advisory Board (SAB) approved with only minor modifications the SAB Committee Report dealing with the ETS Draft Risk Assessment and the Workplace Smoking Policy Guide. The Executive Committee supported the conclusions of the Draft Risk Assessment that ETS is a cause of lung cancer in non-smoking adults and should be classified as a "Group A" carcinogen. Dr. Lippmann explained the recommendations at a press conference.

April 23, 1991 — EPA's SAB finalized the SAB Committee Report dealing with the ETS Draft Risk Assessment and the Workplace Smoking Policy Guide, and issued it to the EPA Administrator. Reportedly, the two documents were slated to undergo revisions by the EPA.

May 30, 1991 — After an unauthorized release of the third document, the Technical Compendium, an article was published by the Associated Press stating that even though the final draft of Technical Compendium had been completed in April, its public release had been delayed indefinitely. According to the article, the EPA had not approved the document and might never approve it.

July 23-24, 1991 — A discussion was scheduled by the EPA's SAB Executive Committee to determine whether the SAB should review the Technical Compendium. The Executive Committee voted not to review the draft Compendium reportedly because the Compendium was not intended as an official EPA document. The SAB recommended that the chapters

of the Compendium be published and thereby undergo a normal peer review before any issuance of the Compendium by the agency. Of the eleven chapters, only one has been published. This chapter deals with ETS and heart disease.

November 15, 1991 — The Nov. 15 1991 issue of Inside EPA reported that the revised risk assessment would not be "released" until March, 1992.

February 24, 1992 — The author responsible for revising the risk assessment presented the status of the document to the EPA SAB on February 24, 1992. According to the presentation, the revised draft document was undergoing internal and "limited external" review which was expected to be completed by March 15, 1992.

SUMMARY OF INDUSTRY RESPONSES TO THE JUNE 1990 FIRST DRAFT EPA RISK ASSESSMENT ON ETS

SUMMARY OF RESPONSES TO SPECIFIC ISSUES PRESENTED TO THE SAB

This document identifies the comments submitted by the Tobacco Institute which respond most directly to the eleven specific questions the SAB has been asked to address in its review of the draft risk assessment ("draft report") on environmental tobacco smoke ("ETS").

A. LUNG CANCER IN ADULTS

1. HAS EPA MET THE REQUIREMENTS STATED IN ITS CARCINOGEN GUIDELINES FOR CHARACTERIZING ETS IN CATEGORY A, I.E., IS THE EVIDENCE SUFFICIENT TO CONCLUDE THAT ETS IS CAUSALLY ASSOCIATED WITH LUNG CANCER?

No. EPA's guidelines/criteria for adequacy of epidemiologic studies (51 Fed.Reg., 33995, 1986) have not been met. In particular, the draft report fails to exclude possible biases, confounders and chance (51 Fed.Reg., 33999). The draft report's criteria for Group A classification are incomplete and inadequate according to EPA's own guidelines (see Tweedie, Clayton, Reasor/Will).

In addition, the draft report has not "given full consideration to all relevant scientific information" (see Clayton, Reasor/Will, Layard/LeVois, Flamm).

The draft report also has not addressed all four "Weight of the Evidence" components (see Clayton, Reasor/Will):

(i) Hazard Identification

- o Failure to characterize the agent in question (ETS)
- o Failure to examine toxicological evidence (animal and short-term tests)
- o Uncritical reliance on "weak association" epidemiology

(ii) Exposure Assessment

- o No characterization of ETS
- o Uncritical reliance on one questionable biomarker
- o No ambient exposure data examined

(iii) Dose-Response Analysis

- o Proper statistical analysis reveals no significant dose-response relation for any epidemiologic study

(iv) Risk Characterization

- o Lacks basis (i-iii above)

2. IS SPOUSAL SMOKING A PROPER MEASURE OF ETS EXPOSURE TO ASSESS LUNG CANCER RISK?

No. Spousal smoking is not a direct quantitative measure of exposure (see Layard/LeVois, Tweedie). In addition, the definition of "spousal smoking" itself differs among studies (see Tweedie).

Spousal smoking does not represent total exposure (see Layard/LeVois, Tweedie) and lends itself to confounders which correlate with characteristics of smoking families (see Butler).

3. ARE THE DIFFERENCES IN RELATIVE RISK OBSERVED BETWEEN STUDIES IN THE U.S. AND THOSE OVERSEAS OF CONCERN, AND IF SO, TO WHAT DEGREE?

Yes. A significant difference between U.S. and overseas studies has been reported. The studies in the U.S. are and have always been statistically insignificant (overall relative risk estimates, 0.99-1.2 for U.S. studies) (see Tweedie, Fleiss). The variation in genetic and lifestyle factors is important between foreign and U.S. populations (see Switzer):

- o Use of cooking and heating fuels (wood and coal burning);
- o Differences in diet;
- o Different rates of lung cancer;
- o Different environmental influences (e.g., housing).

4. IS META-ANALYSIS AN APPROPRIATE TOOL TO USE IN THE DOCUMENT AND HAS IT BEEN APPLIED CORRECTLY? HAVE THE EPIDEMIOLOGICAL STUDIES BEEN PROPERLY EVALUATED AND COMBINED USING THIS TECHNIQUE?

Perhaps. However, EPA has no guidelines for meta-analysis. The use of meta-analysis in the draft report is an inappropriate application of the technique (see Fleiss/Gross). Minimally, the quality of the studies should have been critically assessed prior to combination in a meta-analysis (see Fleiss, Switzer).

Meta-analysis may have been appropriate if certain conditions are applied, such as similarity in study design, common methods of case-control selection, characterization of exposure, and control for effects of confounding and bias in individual studies (see Fleiss, Switzer).

5. (a) HAVE THE MOST IMPORTANT CONFOUNDERS BEEN PROPERLY ADDRESSED? (b) HAS THE ISSUE OF MISCLASSIFICATION (CLASSIFYING CURRENT AND FORMER SMOKERS AS NEVER SMOKERS) BEEN ADEQUATELY ADDRESSED AND THE PROPER ADJUSTMENTS MADE? (c) ARE THERE OTHER CONFOUNDERS WHICH COULD BE ADDRESSED IN GREATER DETAIL?

(a) Although the EPA Guidelines stipulate that confounders must be ruled out, the draft risk assessment fails to consider any confounders. Numerous confounders, some of which correlate with smoking families, exist; all confounders should have been critically addressed in the draft risk assessment (see Butler).

(b) The correction for misclassification is mathematically flawed (see Lee).

(c) Other sources of bias were ignored:

- o publication bias;
- o recall (exposure) bias (see Layard/LeVois).

In addition, the most important confounders which were not considered and which may correlate with smoking include:

- o diet;
- o cooking/heating fuels;
- o family history of lung cancer (see Butler).

6. DOES THE DOCUMENT CHARACTERIZE THE UNCERTAINTIES, BOTH IN THE WEIGHT-OF-EVIDENCE AND THE NUMBER OF ATTRIBUTABLE DEATHS, APPROPRIATELY?

No. The draft risk assessment did not use weight-of-evidence criteria (e.g. ignored toxicology, etc.) (see Flamm). The weight-of-evidence approach in the draft risk assessment is inadequate; numerous uncertainties were not addressed (see Flamm). In addition, existing models for risk characterization of ETS differ by several orders of magnitude (see Layard, LeVois).

7. (a) HAS THE QUANTITATIVE RISK OF LUNG CANCER BEEN PROPERLY ASSESSED? (b) WOULD IT BE MORE PROPERLY ASSESSED BY A DOSE RESPONSE ASSESSMENT USING EITHER COTININE OR RESPIRABLE SUSPENDED PARTICULATES AS SURROGATE MEASURES OF EXPOSURE (APPENDIX C)? (c) WOULD MODELING APPROACHES (APPENDIX D)? (d) SHOULD A DOSE-RESPONSE MODEL BE DEVELOPED FOR ETS-RADON INTERACTION EFFECTS?

(a & b) No. Cotinine is a poor quantitative marker for ETS exposure; research on respirable suspended particulate (RSP) deposition in nonsmokers is virtually nonexistent (see deBethizy). The quantitative risk characterization in the

draft risk assessment is not justified by the weight-of-evidence (see Clayton, Flamm).

(c) No. Modeling approaches are limited by adequacy of input variables.

(d) Information in the EPA-commissioned ETS/Radon study was not addressed in the draft report.

8. SHOULD THE DRAFT REPORT ATTEMPT TO DISTINGUISH BETWEEN THE EFFECTS OF HOME VS. WORKPLACE EXPOSURE TO ETS?

Yes, because the eight epidemiological studies examining workplace exposure do not provide support for the draft report's claim of increased risk (see Tweedie, Lee, Layard/LeVois).

B. RESPIRATORY DISORDERS IN CHILDREN

1. HAS THE WEIGHT-OF-EVIDENCE FOR ETS RELATED RESPIRATORY DISORDERS IN CHILDREN BEEN PROPERLY CHARACTERIZED? A DRAFT REPORT WITH A DETAILED DESCRIPTION AND ANALYSIS OF 26 RECENT STUDIES HAS RECENTLY BEEN PREPARED AND IS ENCLOSED. IT IS IN A FORM SIMILAR TO THAT OF APPENDIX A. SHOULD IT BE INCLUDED IN A REVISED REPORT AS APPENDIX E?

No. At least 25 relevant studies were omitted from the draft risk assessment (see Hood/Witorsch/Witorsch, Huber). The draft report transmitting the 26 studies did not reference any critical analysis of the included studies. Since the draft report transmitting the 26 recent studies was not made available for public comment, it should not be included as an appendix. At a minimum, the entire draft risk assessment should be revised and made available for public review prior to the addition of a new appendix.

2. HAVE CONFOUNDERS IN THE EPIDEMIOLOGIC STUDIES BEEN ADEQUATELY ADDRESSED?

No. The draft report's treatment of confounders is inadequate (see Huber, Hood/Witorsch/Witorsch). Important confounders include:

- o use of gas stoves;
- o history of respiratory illness;
- o viral infections (Respiratory Syncytial Virus);
- o familial factors/heredity.

3. SHOULD A META-ANALYSIS APPROACH BE ATTEMPTED AS IN THE LUNG CANCER ANALYSIS?

No. Different protocols, study designs, methods and analyses preclude the application of meta-analysis (see Huber, Hood/Witorsch/Witorsch).